AMENDMENTS TO THE DRAWINGS

The attached sheet of drawings includes changes to Figure 8B, which has been amended to include the labels "i," "ii," "iii," and "iv" in the appropriate panels of the figure.

REMARKS

Status of the claims

Claims 1, 3-16, 18-31, 33, 34, 36-41, 43, 44, 46-57 and 59-65 are pending. Claims 1, 3, 16, 18-31, 33-34, 36-41, 43-44, and 46-56 were previously withdrawn from consideration as drawn to non-elected inventions, and have been rejoined. Claims 1, 3-16, 18-31, 33, 34, 36-40, 57 and 59-65 are allowed. Claims 41, 43, 44, and 46-56 are rejected. By virtue of this response, claim 50 has been amended.

With respect to claim amendments, Applicants have not dedicated to the public or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Objection to the Drawings

Fig. 8B is objected to because the labels "i," "ii," "iii," and "iv," are referred to in the description of the drawing, and such labels do not appear in the figure. An amended figure is submitted herewith with each panel including the appropriate label, thereby obviating the objection.

Rejection under 35 U.S.C. §112, first paragraph

Claims 41, 43, 44, and 46-56 are rejected under 35 U.S.C. 112, first paragraph, as allegedly not enabled. Applicants respectfully traverse this rejection.

The Examiner states that it would require undue experimentation to practice the claimed method with respect to treating tumors of the muscular layer of the bladder by administration of polynucleotides to the luminal surface of the bladder by intravesicular administration. In response, Applicants provide herewith two references that teach treatment of bladder tumors as claimed in the

rejected claims, Wu et al. (2003) *Clinical Cancer Research* 9:4522-4528 and Wu et al. (2004) *Clinical Cancer Research* 10:6977-6984. These two references are submitted in a Supplemental Information Disclosure Statement filed concurrently herewith.

Wu et al. (2003) *Clinical Cancer Research* 9:4522-4528 describe a study to assess cytokine gene transfection in bladder tumor cells and therapeutic efficacy *in vivo* in an orthotopic mouse bladder cancer model that closely represents the physiological features of human bladder cancer (see abstract and page 4523, left column, third paragraph), using a transfection composition as recited in claim 57. To assess *in vitro* and *in vivo* cytokine gene transfection, a transfection composition comprising DOTAP (as cationic lipid), methyl-β-cyclodextrin (MBC), and plasmid DNA (see page 4523, sections "*In Vitro* Cytokine Gene Transfection and Measurement by ELISA" and "Intravesical Gene Transfection") was used. Notably, this composition contained the same amounts of DOTAP and MBC as the composition described in Example 1 of the present application.

To assess efficiency of *in vivo* transfection and expression, a plasmid comprising a β-galactosidase reporter gene was transfected intravesicularly into normal mouse bladders and into implanted mouse bladder tumors. As shown in Figure 4, in tumors, reporter gene expression was observed in both surface cells and deeper layers, but in normal bladders, expression was confined to the superficial epithelium. Thus, these results show that a composition of the invention may be used to effect intravesical gene transfection to reach both superficial layers of urothelial cells and deeper layers of cells in a bladder tumor. With respect to tumor treatment, mice that underwent cytokine gene therapy in this study exhibited a dramatic decrease in tumor incidence when compared to mice transfected with control plasmid. Tumor incidence decreased from 76.9% in the control group to 15.4-30.8% in the cytokine treatment groups (see abstract and Table 3).

Wu et al. (2004) *Clinical Cancer Research* 10:6977-6984 discloses a study in which the response of bladder tumors to granulocyte macrophage colony-stimulating factor (GM-CSF) was assessed. A bladder tumor cell line was modified to secrete human prostate-specific antigen (PSA) as a biomarker for tumor cell growth. Tumors were implanted in mice, using PSA-secreting tumor cells. A transfection composition as taught in Example 1 of the present application was used for

intravesicular transfection of the tumors using a plasmid encoding GM-CSF (see page 6978, section entitled "Liposome-Mediated Experimental GM-CSF Gene Therapy"; page 6980, section entitled "Response of MB49-PSA Orthotopic Model to GM-CSF Gene Therapy"). Serum levels of PSA were assessed as a measure of tumor growth. PSA levels increased progressively in the control group, while PSA levels started to decrease in some mice after the second week in the treated group (Fig. 4). More than half of the treated mice (10 out of 19) were cured, as indicated by serum PSA levels and confirmed by histology.

Both of the above references describe studies in which intravesicular instillation of a transfection composition as claimed and as taught in the present application, containing a cytokine-encoding polynucleotide, was used to successfully treat bladder tumors. Thus, the claimed methods for treating bladder cancer are enabled by the specification.

The Examiner further states that the claimed methods are not enabled for treatment of bladder cancer with nucleic acids encoding IL-6, IL-9, IL-11, MCSF, HSP, TIMP, or a fibronectin receptor, as recited in claim 50. Solely to expedite prosecution and without acquiescence to the rejection, IL-6, IL-9, IL-11, MCSF, HSP, and fibronectin receptor have been deleted from claim 50 herein, rendering the rejection with respect to these proteins moot.

With regard to the alleged lack of enabling disclosure for tissue inhibitor of metalloproteinases (TIMP), Applicants provide herewith a review article that summarizes the therapeutic potential of the TIMPs from a cancer gene therapeutic point of view, Brand (2002) *Current Gene Therapy* 2:255-271. This reference is submitted in a Supplemental Information Disclosure Statement filed concurrently herewith. With regard to *in vivo* efficacy of TIMPs in treatment of bladder cancer, Table 2 on page 260, fourth row from bottom of page, refers to a study by Kawamata et al. (1995), in which TIMP-1 and TIMP-2 were shown to have a significant therapeutic effect *in vivo* in the treatment of bladder tumors. Thus, at the time of filing of the present application, TIMPs were known to be useful for treatment of bladder cancer.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 578762000100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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